REMARKS/ARGUMENTS

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 31-35, 38-40 and 44-47 are pending in this application.

I. Claim Objections

Claim 38 is objected to as allegedly "being a substantial duplicate of claim 33." The Examiner asserts that "[w]hen two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper to object to the claims as being substantial duplicates." (Page 5 of the instant Office Action).

Applicants respectfully note that Claim 38 recites "The isolated nucleic acid of Claim 33 comprising the nucleic acid sequence of SEQ ID NO:305." In contrast Claim 33 recites isolated nucleic acids comprising: the nucleic acid sequence of SEQ ID NO:305; the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:305; or the full-length coding sequence of the cDNA deposited under ATCC accession number 203312. Accordingly, Claim 33 is broader in scope than Claim 38, because it includes sequences that comprise shorter portions of SEQ ID NO:305 than the full length SEQ ID NO:305 sequence recited in Claim 38. Thus the two claims are not substantial duplicates, and inclusion of both is appropriate.

Claim 31 is objected to for reciting "An isolated nucleic acid of encoding." Applicants thank the Examiner for pointing out this typographical error, which has been corrected by amendment herein.

Accordingly, withdrawal of the objections to the claims is respectfully requested.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 31-35, 38-40, and 44-47 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Examiner notes that "the specification teaches that several primary lung tumors exhibited amplification of the PRO1558 gene." However, in assessing the value of these gene amplification data, the Examiner

notes that: "the specification teaches that the negative control consisted of DNA isolated from the *blood* cells of ten normal healthy individuals. However, the specification is silent as to any correlation between DNA isolated from lung cancer and DNA isolated from the blood." Therefore, the Examiner asserts that "one needs to know, *e.g.*, that the claimed sequence is present only in cancer tissue to the exclusion of the corresponding normal tissue", and concludes that "one of ordinary skill in the art would not be able to use the invention in a predictable manner" because "it would require undue experimentation to practice the invention as claimed." (Pages 3-4 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

First of all, as discussed in Applicants' previous Response filed November 12, 2004, Applicants rely on the gene amplification data for patentable utility for the PRO1558 polypeptide. Applicants respectfully submit that SEQ ID NO:305 encoding PRO1558 was amplified in five *lung tumor* and *lung tumor cell lines* (HF-000840, HF-000842, HF-001294, HF-001296 and HF-001299) and one *colon* tumor (HF-000795).

Therefore, contrary to the Examiner's assertion that one of ordinary skill in the art would not able to use the invention in a predictable manner, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung and colon cancers; for example, by using diagnostic methods based on hybridization to such amplified sequences. As the Manual of Patent Examining Procedure (M.P.E.P.) states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)." (M.P.E.P. §2164.01).

The Examiner contends that the "applicants are attempting to compare the expression of PRO1558 in lung tumor specimens versus its expression in a non-related tissue .... [and that] a true negative control would more than likely comprise the analysis of the expression of PRO1558 in the corresponding normal tissue." (Page 3 of the instant Office Action). While Applicants agree with the Examiner that comparing the expression of PRO1558 in lung tumor with the

expression of PRO1558 in normal lung tissue would be a true negative control, Applicants respectfully submit that the negative control as used in the gene amplification in the present application is also considered a true negative control.

Applicants submit that the gene amplification data were obtained by comparing DNA from a variety of primary tumors, including breast, lung, colon, rectum, kidney, testis, lymph node and parathyroid tumors, and various tumor cell lines with pooled DNA from healthy donors. (See PCT/US00/03565, the priority of which is claimed in the present application). In addition, as the Examiner noted, the samples for the negative control were obtained from blood cells of healthy individuals, as is usual in similar gene amplification assays. It appears to the Applicants that the Examiner's concern is that the positive results of the present application are artifacts caused by the different genetic compositions between the solid tissue and blood. However, the fact that the PR1558 gene was only amplified in six of the lung and colon tumors and lung cell lines, but not in the control sample or in the other tumors or tumor cell lines (*e.g.*, breast tumor) clearly indicates that this is not the case. Otherwise, the PRO1558 gene would be expected to be amplified in all solid tumor tissues.

The Examiner states that "it is unclear if the relevant diagnostic art typically engages in such experimentation." (Page 4 of the instant Office Action). The Examiner further asserts that there is allegedly "no evidence" that the negative control taught in the specification is a true negative control.

Applicants respectfully point out that the negative control taught in the specification was known in the art at the time of filing, and accepted as a true negative control as demonstrated by use in peer reviewed publications. For example, in Pitti *et al.* (Nature 396:699-703 (1998); copy enclosed), the authors used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumours, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific

expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.* (Int. J. Cancer 78:661-666 (1998); copy enclosed), the authors used the quantitative TaqMan PCR assay to study gene amplification of *myc*, *ccnd1* and *erbB2* in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control.

The art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments of the type described in the specification. Therefore, no further experimentation would be required for one of ordinary skill in the art to use the invention in a predictable manner.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection of Claims 31-35, 38-40, and 44-47 under 35 U.S.C. §112, first paragraph.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 31-32 and 34-35 are further rejected under 35 U.S.C. §112, first paragraph, because allegedly "the specification, while being enabling for an isolated nucleic acid comprising SEQ ID NO:305, does not reasonably provide enablement for isolated nucleic acids encoding polypeptides of SEQ ID NO:306." (Page 5 of the instant Office Action).

The Examiner asserts that "the increased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity, or role in cancer." (Page 6 of the instant Office Action). The Examiner further cites Konopka *et al.* and Lewin in support of the assertion that "degenerate or variant polypeptides do not necessarily predict protein expression."

Applicants respectfully point out that the instant claims are directed to nucleic acids, not polypeptides. Given the described use for the claimed nucleic acids, there is no need to discuss uses for the encoded polypeptides. Thus the discussion of protein expression levels is irrelevant.

The Examiner further asserts that "it would not be predictable that all degenerate nucleotides encoding variant polypeptides with sequence similarity to the amino acids of SEQ ID NO:306 would be useful for diagnostic purposes, especially in analyzing gene amplification in tumors such as lung or colon tumors." (Page 6 of the instant Office Action). Applicants respectfully point out that the claims recite nucleic acids encoding polypeptide variants "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors." That is, the instant application does not claim all possible degenerate nucleic acid sequences encoding polypeptide variants having at least 95% amino acid sequence identity to SEQ ID NO:306, but only those nucleic acid sequences which are, like SEQ ID NO:305, amplified in lung and colon tumors. Thus the recited nucleic acid variants have the same utility, in the diagnosis of lung and colon tumors, as SEQ ID NO:305.

The instant specification provides ample guidance to allow one of ordinary skill in the art to identify, make and use those variants covered by the claims. Example 143 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO1558 protein is amplified in lung or colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 302, line 4, to page 305, line 4). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO1558 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 354, line 30 to page 358, line 34) and methods of preparing the PRO polypeptides (see page 358, line 35 and onward).

Therefore, Applicants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a nucleic acid sequence which encodes a variant polypeptide to determine whether it is amplified by the methods set forth in Example 143. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence

to identify nucleic acids encoding polypeptide sequences with at least 95% identity to SEQ ID NO:306. Therefore, one skilled in the art would know exactly how to make and use the claimed nucleic acids for the diagnosis of lung and colon cancers (for example, by using diagnostic methods based on hybridization to such amplified sequences) without undue experimentation.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection of Claims 31-32 and 34-35 under 35 U.S.C. §112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C61**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 12, 2005

By: _____
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